**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

| | | |
|---|---|---|
| In re application of: | ) | Examiner: Landsman Robert S. |
| | ) | |
| Audrey GODDARD, et al. | ) | Art Unit: 1647 |
| | ) | |
| Application Serial No. 09/997,542 | ) | Confirmation No: 7269 |
| | ) | |
| Filed: November 15, 2001 | ) | Attorney's Docket No. 39780-2730 P1C26 |
| | ) | |
| For: **PRO1281 ANTIBODIES** | ) | **Customer No.** 77845 |

---

**FILED VIA EFS ON JUNE 11, 2008**

**ON APPEAL TO THE BOARD OF PATENT APPEALS AND INTERFERENCES APPELLANTS' REPLY BRIEF**

**MAIL STOP APPEAL BRIEF - PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On September 18, 2007, the Examiner made a Final rejection to pending Claims 119-121 and 123. A Notice of Appeal was filed on December 18, 2007 and an Appellants' Appeal Brief was subsequently filed March 18, 2008.

An Examiner's Answer was mailed on April 21, 2008. The following constitutes Appellants' Reply Brief in response to the Examiner's Answer and is timely filed within the period set for response. This Reply Brief is accompanied by a Request for Oral Hearing.

## ARGUMENTS

### I. *Claim Rejections Under 35 U.S.C. §101 and §112, First Paragraph*

Concerning the rejection of Claims 119-121 and 123 under 35 U.S.C. §101 as allegedly lacking a specific, substantial and credible asserted utility or a well established utility, in his Answer, the Examiner cites the following arguments:

(1) The Examiner did not find the Goddard declaration persuasive and says that "there is no statistical analysis disclosed, nor any formula disclosed showing how the data was analyzed in order to determine the significance of the amplification" (Examiner's Answer, page 5) and that it "does not teach the level of reproducibility or the level of reliability of the results" (Examiner's answer, page 6). The Examiner further asserts that "the declaration addresses whether the dCt values are significant, and not whether or not gene amplification correlates with polypeptide levels (Examiner's answer, page 6). The Examiner also argues that Dr. Goddard, the expert, has interest in the outcome of the case because Dr. Goddard is employed by the assignee and is an inventor in this application (Examiner's answer, page 6). The Examiner addresses the pooled blood controls used in the gene amplification assay and asserts that the controls were not matched, non-tumor lung samples, but rather pooled DNA samples from blood of healthy subjects. The Examiner asserts that "the fact that only two colon tumors (CT2 and CT12) were tested makes it difficult to conclude that it would be more likely than not that other colon tumors could be identified in this manner" (page 6 of Examiner's Answer).

(2) The Examiner alleges that the Ashkenazi declaration actually supports the Examiner's position in that it provides further evidence that gene amplification does not correlate with increased mRNA/polypeptide levels (page 11 of the Examiner's Answer).

(3) The Examiner asserts that references such as Pennica *et al.*, Konopka *et al.*, Sen *et al.*, Godbout *et al.*, and Li *et al.* constitute strong opposing evidence for the claimed polypeptides having utility and enablement, based on the presumption that the claimed polypeptides are also overexpressed following gene amplification (pages 6-9 of the Examiner's Answer). Referring to Sen, the Examiner alleges that, in general, non-cancerous epithelial tissues are frequently aneuploid, and thus an increase in genomic DNA is not diagnostic of cancer. The Examiner also quotes Godbout as stating: "*It is generally accepted that co-amplified genes are not over-*

*expressed unless they provide a selective growth advantage to a cell...*" and thereby inquires whether Appellant can show evidence for PRO1281 providing a selective growth advantage to a cell (page 8 of Examiner's Answer).

(4) Regarding the supportive references Orntoft *et al.*, Hyman *et al.* and Pollack *et al.*, made of record by the Appellants, and which clearly address gene amplification, the Examiner considers them flawed. The reasons cited were: Orntoft *et al.* only compared levels of about 40 well-resolved an focused on abundant proteins; Hyman *et al.* found 44% of highly amplified genes showed overexpression at the mRNA level, and 10.5% of highly overexpressed genes were amplified and even at this level of high amplification and high overexpression, the two did not correlate; Pollack *et al.* is also limited to highly amplified genes and used a different method to evaluate their results (pages 9-10 of Examiner's Answer).

Appellants strongly disagree with each of the Examiner's arguments on a number for grounds. The Examiner's arguments will be addressed in the order they are listed above.

**Reply to the Examiner's arguments**

(1) The Examiner makes the rejection that "there is no statistical analysis disclosed, nor any formula disclosed showing how the data was analyzed in order to determine the significance of the amplification" (Examiner's Answer, page 5). The Examiner's Answer concludes that "Dr. Goddard, the expert, has interest in the outcome of the case because Dr. Goddard is employed by the assignee and is an inventor in this application (Examiner's Answer, page 6). The Examiner asserts that "the fact that only two colon tumors (CT2 and CT12) were tested makes it difficult to conclude that it would be more likely than not that other colon tumors could be identified in this manner" (page 6 of Examiner's Answer).

Appellants submit that the Examiner is applying a standard that is not legally correct. The law, as it is reflected in the M.P.E.P. and the Utility Guidelines does not require that the Appellant show a positive result in a statistically large percentage of the tissue samples studied in order to make an assertion of utility. The above remarks by the Examiner are a clear indication that the Examiner applies a standard that might be appropriate, if the issue at hand were the regulatory approval of a diagnostic assay based on the overexpression of PRO1281 in colon tumor, but is fully inappropriate for determining if the "utility" standard of the Patent Statute is met. The FDA reviewing an application for a new diagnostic assay will indeed ask for actual numerical data, statistical analysis, and other specific information before a diagnostic assay is approved. However, the Patent and Trademark Office is not the FDA, and the standards of patentability are not the same as the standards for market approval. It is well established law that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to be marketed in the United States. *Scott* v. *Finney,* 34 F.3d 1058, 1063,32 USPQ2d 1115, 1120 (Fed. Cir. 1994). Indeed, in *Nelson* v. *Bowler,* 626 F.2d 853,856,206 USPQ 881, 883 (CCPA 1980), the Federal Circuit found that the identification of a pharmacological activity of a compound provides an "immediate benefit to the public" and satisfies the utility requirement. This logically applies to a diagnostic utility as well. The identification of a diagnostic utility for a compound should suffice to establish an "immediate benefit to the public" and thus to establish patentable utility.

Further, the Goddard Declaration was presented to show what delta Ct values were considered significant in the TaqMan" assay. The deltaCt values for PR01281 of at least 1.07 to 1.15 Ct units, which correspond to 2.099 fold to 2.219-fold amplification in primary colon tumors, were considered significant according to the Goddard declaration. The formula for showing how the data was analyzed has been clearly disclosed in the specification in Example 170, page 539. As explained in the passage on page 539, lines 37-39, "the results of TaqMk™ PCR are reported in ~Ct units. One unit corresponds to one PCR cycle or approximately a 2fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Table 9C indicates that PR01281 showed approximately 1.07-1.15 deltaCt units which corresponds to $2^{1.07} - 2^{1.15}$-fold amplification or 2.099 fold to 2.219-fold amplification in colon tumors, which is significant and thus the PR01281 gene has utility as a diagnostic marker of human colon cancer.

Further, Dr. Goddard's declaration is based on Dr. Goddard's personal experience handling large databases of human tumor samples in the SPDI project and on personal experience with the Taqman" assay, as is clearly disclosed in the Declaration. The Examiner cannot disregard this declaration simply because Dr. Goddard works for the Assignee. Instead, the Examiner has to view the statements in the declaration with the total evidence presented in this case. The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew (*In re Rinehart,* 531 F.2d 1084, 189 USPQ 143 (C.c.P.A. 1976); *In re Piasecki, 745*F.2d. 1015,226 USPQ 881 (Fed. Cir. 1985)). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument."( *In re Alton,* 37 USPQ2d 1578, 1584 (Fed. Cir 1996) (quoting *In re Oetiker,* 977 F.2d 1443, 1445,24 USPQ2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton,* "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an Examiner (*In re Alton, supra.).* Appellants also respectfully draw the Examiner's attention to the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the

significance or meaning of the facts offered." Appellants submit that the Patent Office has failed to provide substantial evidence for disregarding the Goddard Declaration.

Regarding the rejection of pooled controls (addressed in the Goddard Declaration), Appellants respectfully point out that Pennica *et al.* teaches the exact same "pooled normal blood controls" as that used in the instant gene amplification assay (for instance, see page 14718, column 1 and Figure 5 of Pennica *et al.*). Further, the references Bieche *et al.* and Pitti *et al.*, submitted as Exhibits F and G with the Goddard Declaration, also used "pooled normal blood controls" as control. For instance, in Pitti *et al.* the authors used the same quantitative TaqMan PCR assay and pooled normal blood controls described in the instant specification, to study gene amplification in lung and colon cancer of DcR3, a decoy receptor for Fas ligand. Pitti *et al.* analyzed DNA copy number "in genomic DNA from 35 primary lung and colon tumors, relative to pooled genomic DNA from peripheral blood leukocytes (PBL) of 10 healthy donors." (Page 701, col. 1). The authors also analyzed mRNA expression of DcR3 in primary tumor tissue sections and found tumor-specific expression, confirming the finding of frequent amplification in tumors, and confirming that the pooled blood sample was a valid negative control for the gene amplification experiments. In Bieche *et al.*, the authors used the quantitative TaqMan PCR assay to study gene amplification of myc, ccnd1 and erbB2 in breast tumors. As their negative control, Bieche *et al.* used normal leukocyte DNA derived from a small subset of the breast cancer patients (page 663). The authors note that "[t]he results of this study are consistent with those reported in the literature" (page 664, col. 2). Thus, contrary to the Examiner's allegations, Pennica *et al,* Pitti *et al.* and Bieche *et al.* in fact, confirm the validity of use of the "pooled blood control" as a negative controls, and indicate that this control was widely utilized in the art at the time of filing of the instant application.

(2) The Examiner alleges that the Ashkenazi Declaration actually supports the Examiner's position in that it provides further evidence that gene amplification does not correlate with increased mRNA/polypeptide levels. This position of the Examiner is based on a complete misinterpretation of the Ashkenazi Declaration, its teachings and the arguments presented by the Appellants regarding this Declaration. Appellants fail to see how the Ashkenazi Declaration could support the Examiner's arguments when Appellants clearly stated that, even if there were no correlation between gene amplification and increased mRNA/protein expression, (**which**

**Appellants expressly do not concede to**), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Appellants submit that, based on the teachings of the Ashkenazi Declaration and the Hanna and Mornin reference (both previously made of record), one of skill in the art would have known that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, were not to be over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu. Again, the presentation of this explanation in support of utility is not to be interpreted as a submission of a lack of correlation between DNA and/or mRNA/ protein levels.

(3) Appellants have already discussed the references Pennica *et al.*, Sen *et al.*, Godbout *et al.*, Bea *et al.* and Li *et al.* in great detail throughout prosecution and in their Appeal Brief filed March 18, 2008; these discussions and arguments are hereby incorporated by reference.

Briefly, the teachings of Pennica *et al.* are specific to *WISP* genes, a specific class of closely related molecules. Pennica *et al.* showed that there was good correlation between DNA and mRNA expression levels for the *WISP-1* gene but not for *WISP-2 and WISP-3* genes. The fact that, for two out of three specific molecules there seems to be no correlation between gene amplification and/or mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. As discussed throughout prosecution, the standard is not absolute certainty. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression for genes in general. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression* . . . " (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added). Accordingly, Appellants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between gene amplification and over-expression of mRNA or polypeptides in most genes, in general. Therefore, the teachings of Pennica *et al.* are not directed towards genes in general but to a single gene or genes

within a single family and thus, their teachings cannot support a general conclusion regarding a correlation between gene amplification and mRNA or protein levels.

In fact, in the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Appellants submit that when the proper legal standard is applied, one of skill in the art should reach the conclusion, based on the amplification data for the PRO1281 gene, that the PRO1281 polypeptide is concomitantly overexpressed, and that the present application discloses at least one patentable utility for the claimed PRO1281 polypeptides. Accordingly, one of ordinary skill in the art would also understand how to make and use the recited polypeptides for the diagnosis of lung and colon cancer without any undue experimentation.

Regarding the art exemplified by Sen *et al.*, Appellants' maintain their position that Sen still supports their case for the reasons outlined in their Appeal Brief filed March 18, 2008, which is hereby incorporated by reference. Briefly Appellants maintain that, even if the amplification of the PRO1281 gene were due to chromosomal aneuploidy (which Appellants expressly do not concede to), since there is utility for an aneuploid gene at least as a marker for cancer or precancerous cells or damaged tissue, one skilled in the art would find it entirely reasonable that PRO1281 is useful in the early detection of colon cancer.

The Examiner contends that the Li article constitutes strong opposing evidence for the presumption that the claimed polypeptides are also overexpressed following gene amplification. Appellants respectfully disagree. The Li article was discussed extensively in the Appeal Brief filed March 18, 2008; these discussions and arguments are hereby incorporated by reference. In the article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. In the instant case for PRO1281, as discussed in the Goddard Declaration (of record), an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0 (which is a higher threshold that Li's 1.40). The PRO1281 gene showed significant amplification of **2.099 fold to 2.219 fold amplification in two colon tumors**, and thus fully meets the Goddard standard as well as the Li standard. Appellants further note, and it is not surprising that, in the Li *et al.* reference, by using a lower threshold of 1.4 for considering gene amplification, a higher number of genes not showing corresponding increases in mRNA

expression were found. Nevertheless, the results of Li *et al.* do not conclusively disprove that a gene with a substantially higher level of gene amplification, such as PRO1281, would be expected to show a corresponding increase in transcript expression. Therefore Li does not constitute opposing evidence.

In response to Applicants' argument that the discordance may reflect methodologic differences, the Examiner asserts that "Li *et al.* did not limit their studies to genes that were amplified at less than 2-fold." In support of this assertion, the Examiner cites the first paragraph of the Supplemental Material. (Page 9 of the Examiner's Answer). Applicants respectfully point out that the Examiner has misinterpreted the methodology disclosed in the supplemental material. The evidence cited by the Examiner pertains to the inclusion criteria of the probes used for defining amplicons. In the second paragraph entitled "Relationship between genomic copy number and gene transcript level", the authors state that "[f]or each gene, the CGH data were represented by a vector that was labeled '1' for genomic overrepresentation (including amplification) ratio greater than 1.40 and '0' for no genomic overrepresentation." Nevertheless, the Examiner acknowledges that the alleged 2-fold amplification criteria would only apply to some of the samples. The Examiner has not established that a correlation does not exist in samples based solely on this threshold.

Based on Godbout et al., the Examiner requests "that the protein encoded by the PRO1281 gene would confer any selective advantage on a cell expressing it." in the Examiner's answer; in other words, the Examiner requests Appellants to show the mechanism by which the claimed protein acts within the cell. However, Appellants respectfully remind the Board that demonstration of the mechanism is not a requirement for attaining that utility. Appellants believe that such a requirement is a heightened utility standard imposed by the Examiner. In fact, as stated by the Federal Circuit, "it is not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *In re Cortwright*, 165 F.2d 1353, 1359 (Fed. Cir. 1999). The Federal Circuit has also stated that "[a]n invention need not be the best or only way to accomplish a certain result, and it need only be useful to some extent and in certain applications: "[T]he fact that an invention has only limited utility and is not operable in certain applications is not grounds for finding lack of utility." *Envirotech Corp. v. Al George, Inc.* 730 F.2d 753,762, 221 USPQ 473,480 (Fed. Cir. 1984)." Hence this rejection is improper.

(4) The Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and Godbout *et al.* references were presented during prosecution to show that, in general, gene amplification increases mRNA expression. As Appellants have acknowledged, the correlation between changes in mRNA level and protein level is not exact, and there are exceptions (*see, e.g.,* abstracts submitted in the IDS filed on August 2, 2006 as Exhibit 21). However, Appellants have submitted with their Preliminary Amendment of August 2, 2006 over 100 references in addition to the declarations and references already of record which support Appellants' asserted utility, either directly or indirectly. This included references that studied single genes or gene families, multiple or large families of genes, and included studies that a wide variety of techniques, including gene amplification and microarray. Regardless of the techniques employed, **by and large**, increased gene levels generally correlated well with increased mRNA and /or protein levels, even if accurate predictions of proteins could not be made. As discussed throughout prosecution, the law does not require the existence of a "necessary" correlation between DNA/mRNA and protein levels, or that protein levels be "accurately predicted." In fact, authors in several of the cited references (cited both, by the Examiner, and by Appellants) themselves acknowledge that there is a general correlation between protein expression and transcript levels and DNA levels, which meets the "more likely than not standard." Therefore Appellants have explored this issue thoroughly throughout prosecution in the vast number of references presented in this case and the evidence should be viewed as a whole.

Regarding the Examiner's contention that references Orntoft *et al.*, Hyman *et al.*, Pollack *et al.* are flawed because, allegedly, their studies were directed to highly amplified genes or abundant proteins, Appellants have submitted that PRO1281 is significantly amplified (according to the Goddard Declaration) throughout prosecution. Appellants believe that this significantly amplified DNA would more likely than not result in a higher expression of PRO1281 protein, according to the teachings of many references including Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, Godbout *et al.*

Collectively, Appellants submit that the Examiner's concerns in this rejection are misplaced and cannot properly form the basis for utility rejections of the present claims.

## II. *Claim Rejections Under 35 U.S.C. §112, First Paragraph - Enablement*

Claims 28-32 are rejected under 35 U.S.C. §112, first paragraph, for containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains or with which it is most nearly connected, to make and/or use the invention.

Appellants disagree for the reasons previously presented in Appellants Brief and in the discussion presented herein under Claim Rejections under 35 USC §101. Appellants submit that, as discussed above, antibodies to the PRO1281 polypeptides have utility in the diagnosis of colon cancer. Based on such a utility, one of skill in the art would know exactly how to use the claimed antibodies, for example, for diagnosis of cancer without any undue experimentation.

## III. *Claim Rejections Under 35 U.S.C.§102*

A. Appellants maintain, for the reasons set forth in the Appeal briefs filed January 26, 2006 and March 18, 2008, that priority application, U.S. provisional application 601141,037 has utility based on the gene amplification assay, and thus Claims 119-121 and 123 are entitled to the priority date of June 23, 1999. Therefore, Tang et al. is not prior art.

B. Appellants maintain, for the reasons set forth in the Appeal briefs filed January 26, 2006 and March 18, 2008, that priority application, U.S. provisional application 601141,037 has utility based on the gene amplification assay, and thus Claims 119-121 and 123 are entitled to the priority date of June 23, 1999. Therefore, Baker et al. is not prior art.

## IV. *Claim Rejections Under 35 U.S.C.§103*

Appellants maintain, for the reasons set forth in the Appeal brief filed January 26, 2006 and March 18, 2008, that priority application, U.S. provisional application 601141,037 has utility based on the gene amplification assay, and thus Claims 119-121 and 123 are entitled to the priority date of June 23, 1999. Therefore, Tang *et al.* is not prior art and therefore this 103 rejection falls based on Tang *et al.* Further, Weimann *et al.* does not teach the instantly claimed subject matter and hence this reference also falls. Therefore, this rejection under 103 should be withdrawn.

## CONCLUSION

For the reasons given above, Appellants submit that present specification clearly describes, details and provides a patentable utility for the claimed invention. Moreover, it is respectfully submitted that based upon this disclosed patentable utility, the present specification clearly teaches "how to use" the presently claimed polypeptide. As such, Appellants respectfully request reconsideration and reversal of the outstanding rejection of Claims 119-121 and 123.

The Commissioner is authorized to charge any fees which may be required, including extension fees, or credit any overpayment to Deposit Account No. **07-1700** (referencing Attorney's Docket No. **123851-181895 (GNE-2730 P1C26)**.

Respectfully submitted,

Date: June 11, 2008

Christopher De Vry
Reg. No. 61,425

**Goodwin Procter LLP**
Counselors at Law
135 Commonwealth Drive
Menlo Park, CA 94025
Telephone: 650.752.3100
Facsimile: 650.853.1038